IN THE DRAWINGS

Replacement drawing sheets are supplied herewith. The replacement drawings sheets are submitted to address the objections raised in the "Notice of Draftperson's Patent Drawing Review".

REMARKS

Claims 1, 2, and 8 are amended. Claims 1-11 are pending in this application.

The amendments to claim 1 and 2 are supported by the specification as filed, for example, at page 9, line 36 and at page 10, lines 14-21.

The amendments to claim 8 are supported by originally-filed claim 8.

I. The Objection under 35 U.S.C. § 132

The Examiner objected to the 01/02/02 Amendment, which was mailed 10/24/01, alleging that it introduced new matter into the disclosure with the amendment of the paragraph at page 16, lines 27-34. The amendment concerned switching the assignment of the marks for HRP activity of intact cells and cytosol in Figure 4. Following the Examiner's suggestion, Applicant has included herewith a Declaration from Dr. Selbo, the individual who performed the experiments in question (hereinafter the Selbo Declaration). Copies from the lab notebook in which the results were recorded are included with the Selbo Declaration. The Selbo Declaration presents evidence of the correct assignment of the marks, which is indicated in the objected-to Amendment. Thus, Applicant respectfully requests that the Examiner withdraw the objection to the above-identified Amendment and enter that portion of the above-identified Amendment that has been objected to.

II. The 35 U.S.C. § 112, Second Paragraph, Rejection of Claim 8

The Examiner rejected claim 8 under 35 U.S.C. § 112, second paragraph, alleging that claim 8 is indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 8 has been amended to correct the typographical error noted by the Examiner. Thus, the Examiner is respectfully requested to withdraw the rejection of claim 8 under 35 U.S.C. § 112, second paragraph.

III. The 35 U.S.C. § 112, First Paragraph, Rejection of the Claims

The Examiner rejected claims 1-11 under 35 U.S.C. § 112, first paragraph, alleging that those claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to

make and/or use the invention. The Examiner also rejected claims 1-11 under 35 U.S.C. § 112, first paragraph, alleging that those claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. As these rejections may be maintained with respect to the pending claims, they are respectfully traversed.

A. The Enablement Rejection

The Examiner alleges that the specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Independent claim 1 has been amended to recite a method of expressing an antigenic molecule on the surface of a cell, said method including introducing a molecule into the cell cytosol by photochemical internalization, wherein said molecule, or a part thereof of sufficient size to generate an immune response, is subsequently presented on the surface of said cell by class I MHC molecules. Claims 2-11 depend directly or indirectly from claim 1.

To be enabling, the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 42 U.S.P.Q.2d (BNA) 1001, 1004 (Fed. Cir. 1997). The scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *Id.* Whether making or using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a matter of degree. *PPG Industries Inc. v. Guardian Industries Corp.*, 156 F.3d 1351, 37 U.S.P.Q.2d (BNA) 1618, 1623 (Fed. Cir. 1996). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation must not be unduly extensive. *Id.* Applicants assert that the present specification teaches one skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

One of the Examiner's main concerns appears to be that chromium release as shown in Example 2 of the specification and the Declaration of Inventor Høgset (hereinafter the Høgset Declaration) is an indication of cell death only and can not be considered to comprise a demonstration of the claimed process. Thus, the Examiner remains unconvinced that cell death results from peptide presentation and a specific CTL response. However, the Examiner's

attention is directed to Mukherjee *et al.* (*J Exp Med, 187*, 445 1998) and Okano & Purtilo (*Journal of Immunological Methods, 184*, 149 1995), copies of which are enclosed herewith, which indicate that this test is an art-accepted test for surface presentation.

Mukherjee *et al.* used a CTL clone specific to a particular epitope of the protein EBNA-1 to investigate if that particular epitope was presented on certain cells. Lysis of target cells as assessed by a standard chromium-51 release assay was used as evidence that presentation of that epitope occurred on the surface of those target cells (see, for example, the abstract and page 448, right hand column, lines 24 to 29). The article by Okano & Purtilo refers to the chromium-51 release assay as a conventional method for evaluating Epstein-Barr virus specific CTLs. In both of these publications, the release of chromium is taken as evidence that a specific immune response of a CTL to a cell presenting the correct antigen epitope occurs. Thus, the data of Example 2 is in line with conventional testing for surface expression and the generation of an immune response, where the MART-1 peptide is indeed presented and a CTL response specific to that peptide is induced. In the system that is used in Example 2, the T-cell clone lyses the target cells only if the antigen is presented and, as a consequence, lysis of the target cells shows that the antigen has been presented. This presentation occurs only when photochemical internalization (PCI) has been performed, thus showing that photochemical treatment causes internalization in such a way that presentation in a form appropriate to induce normal immune responses occurs. This indicates that PCI effectively achieves surface presentation of antigenic molecules for the generation of an immune response.

Example 2 demonstrates a presentation mechanism of expression on the surface of the cell by MHC class I molecules and thus shows that PCI connects to this particular presentation system. In other experimental systems, variation may occur in the photosensitizers that are used, the antigenic molecules that are used and the cells which are used. The arguments below however illustrate that the invention would still be expected to work in the manner shown in Example 2 if these parameters were varied.

Cell type

D1 (WO96/07432) shows that photochemical internalization occurs in many cell types. For example, the examples describe transport of proteins into NHIK 3025, V79, H146, COS-7 and OHS cells. The last paragraph on page 11 of D1 indicates that a variety of different

photosensitizers and doses can be used to introduce different molecules into the cytosol of cells. Thus, Example 2 of the present application does not concern the use of an unusual cell, and PCI would be expected to work on a variety of cell types.

Furthermore, Selbo *et al.* (*Int J Cancer*, *87*, 853 (2000); copy enclosed herewith) demonstrates the internalization of MOC 31-gelonin in which the monoclonal antibody MOC31 is conjugated to gelonin. Selbo *et al.* (2000) demonstrates that internalization is effective in five different cell types (NCI-H146, KM20L2, WiDr, T-47D, and THX). Successful internalization is apparent from the figures, which show that the use of the cytotoxic agent gelonin alone is ineffective in reducing protein synthesis and only has this cytotoxic effect once transferred to the cytosol, which is achieved using only PCI. This document also demonstrates the efficacy of two different photosensitizers from internalization, namely, $TPPS_{2a}$ and $AlPcS_{2a}$. Thus, Selbo *et al.* (2000) is a further example of internalization of a protein using the PCI method.

The next question is whether once internalization of the molecule had occurred, one could expect that presentation would occur. The present claims are directed to expression via MHC Class I molecules. Since this machinery has been shown to be effective in presentation of photochemically-internalized molecules, the existence of MHC Class I molecules in the cells would ensure that those cells will achieve effective presentation of photochemically internalized molecules. Thus, the ability of PCI to work in a variety of tested cell types, and the fact that these cells have MHC Class I molecules, will ensure that these cells will allow effective presentation of the internalized molecules (or portions thereof).

Photosensitizers

A variety of photosensitizers have been shown to achieve PCI. For example, D1 describes the use of $TPPS_{2a}$, $AlPcS_{2a}$, and $TPPS_4$. Furthermore Selbo *et al.* (*Photochemistry and Photobiology*, *74*, 303 2001; copy enclosed herewith), shows that 5-aminolevulinic acid (5-ALA) results in PCI. For example, Figure 3 shows that the proteinaceous cytotoxic agent alone does not affect cell viability (solid squares) and that 5-ALA only has an effect on viability as illumination time increases (solid circles), whereas when used in combination (open triangles), cell viability is significantly compromised, illustrative of internalization of the cytotoxic agent. Thus, a variety of different photosensitizers have already been shown to achieve PCI. As mentioned above in connection with cell type, as the PCI is performed on cells with MHC Class

I molecules, internalization and subsequent appropriate presentation will occur with various photosensitizers.

Antigenic molecules

It has been demonstrated that PCI works well with a variety of different classes of substances ranging from low molecular weight drugs, a ras-derived peptide (*i.e.*, a peptide different to MART-1), and proteins. The Examiner is also requested to note that D1 shows the internalization of the proteins gelonin, agrostin, and saporin. Thus, a variety of molecules, including particular proteins, can be internalized. Once internalized, as mentioned above in connection with the various cell types, presentation of peptides via the MHC Class I machinery will occur.

The present invention shows that following internalization (which can be achieved with a variety of molecules, using a variety of means in a variety of cells), appropriate presentation via the MHC Class I machinery occurs. The natural immune responses that flow from the appropriate MHC Class I presentation of peptides are well known and occur as a matter of course once the naturally occurring presentation machinery is in use. Applicant respectfully asserts that the present application needs only to show that after internalization occurs, the internal machinery of the cell can access those internalized molecules and process them appropriately for presentation. This step of presentation after internalization has been shown in Example 2, as the presentation clearly occurs in an appropriate form to elicit a CTL, *i.e.*, immune response. Applicant therefore respectfully submits that all the required elements and the effects of variation in those elements have been shown to work for the present invention across the full breadth of the claim scope which should thus satisfy the enablement requirement.

The Examiner also raised the concern that insufficient information is provided on ensuring that cell death does not occur but rather that internalization occurs. The Examiner appears to be of the opinion that optimizing internalization rather than cell death is unpredictable and that the skilled person is not provided with details of all the factors that should be taken into account and how they should be varied. Applicant respectfully disagrees. PCI is a technique which is described in detail in D1. D1 shows the effect of time of irradiation on internalization, the use of different agents and the use of different concentrations of the molecule to be internalized, which in the particular case of D1 is selected to be a toxin molecule. D1 teaches

that the viability of the cell is retained by modifying the conditions used for internalization accordingly to maximize internalization, but minimize cell death (see the passage bridging pages 2 and 3 in D1). See also, for example, Example 2 in D1 which discusses how to vary the level of survival by appropriate selection of the photosensitizer and the light exposure, and Example 3 which illustrates that light doses control the amount of molecules released into the cytosol. See also Examples 4 and 5 which illustrate that viability of the cells can be largely unaffected. The present application suggests that such variation should be used to maintain viability (see e.g. page 15 from line 19).

Thus, Applicant respectfully submits that the optimization necessary to obtain the appropriate conditions dependent on the light, cell, antigenic molecule and photosensitizer to be used is taught in the art. Furthermore, the optimization is not unpredictable. Higher intensity light or longer irradiation times will lead to more cell damage and hence cell death. Higher photosensitizer doses will lead to higher cell damage and hence cell death. The skilled person needs simply to either increase the levels of these factors until maximum internalization is achieved before significant cell death occurs, or if cell death if occurring, reduce the levels of these factors until that cell death reduces. In all the experiments conducted thus far, as the parameters are initially increased, internalization increases. At some point, however, as the parameters are increased further, cell death increases. Thus, a graph may be plotted showing internalization versus cell death as the parameters are increased. This is what is shown in the Høgset Declaration previously submitted by the Applicant in Figure 2 which shows that transfer of molecules can be achieved with a minimal loss of survival. The skilled person can select an appropriate set of parameters at which maximal internalization has occurred with minimal cell death. Furthermore, this optimization involves routine screening techniques, and routine screening techniques do not constitute undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400, 1406-1407 (Fed. Cir. 1988).

Finally, the Examiner contends that one is not taught how to select a non-toxic versus toxic molecule for transfer. The present invention is not concerned with the selection of molecules for vaccination, merely how best to present such molecules. As such, any molecules suitable for vaccination can be used in the invention, and the skilled person does not need to be taught this or be taught how to make an appropriate selection.

Applicant therefore asserts that the specification fully enables one skilled in the art to use the method of the present invention. The first paragraph of 35 U.S.C. §112 requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims, and this requirement has been met. It is respectfully submitted that the pending claims conform with 35 U.S.C. §112, first paragraph. Therefore, Applicant requests that the Examiner withdraw the 35 U.S.C. §112, first paragraph enablement rejection of the claims.

B. The Written Description Rejection

The Examiner alleged that there is insufficient written description to show that Applicant was in possession of a method of photochemical internalization, as recited in the claims. The Examiner specifically alleges that the term "photoactivating light", as it relates to photochemical internalization, has not been defined.

To satisfy the written description requirement, an Applicant's specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was legally in possession of the elements of the invention sought to be patented, i.e., whatever is claimed. M.P.E.P. § 2163; *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). Furthermore, a patent application need not teach, and preferably omits, what is well known in the art. "Guides for Examination of Patent Applications under the 35 U.S.C. § 112, ¶ 1 'Written Description' Requirement," 66 *Fed Reg* 1099, 1105 (2001). (The absence of definitions or details for well-established terms should not be the basis for rejection for lack of adequate written description); *Spectra-Physics Inc. v. Coherent Inc.*, 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987). In other words, the sufficiency of the specification must be evaluated from the viewpoint of one skilled in the art, who is also in possession of all of the relevant prior art. Thus, an Applicant is not limited to information within the four corners of the specification when called upon to demonstrate that the written description requirement is satisfied.

The Examiner's attention is drawn to D1 and the comments made with regard to D1 hereinabove. Specifically, D1 relates to photochemical internalization. Furthermore, Applicant discusses D1 at page 4, lines 11-21 of the specification, including a discussion of the

"photoactivating light" of D1. Moreover, as the Examiner acknowledges, Applicant's specification describes at page 14 the light used in the in the method of photochemical internalization. The Examiner's attention is also directed to claim 2, which further clarifies the method of claim 1. Therefore, after considering both the disclosures in the specification, and also the information known to the art worker, Applicant respectfully asserts that the specification does convey with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was legally in possession of the elements of the invention sought to be patented. Specifically, Thus, it is submitted that the 35 U.S.C. § 112, first paragraph, written description requirement has been met. Therefore, the Examiner is respectfully requested to withdraw the written description rejection of the claims.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to telephone Applicant's attorney (612-371-2110) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743

Respectfully submitted,
KRISTIAN BERG ET AL.
By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
612-371-2110

Date Aug 11, 2003

By _____
Peter L. Malen
Reg. No. 44,894

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, P.O.Box 1450, Alexandria, VA 22313-1450, on this 11th day of August, 2003.

Patricia A. Hultman _____

Name Signature